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## A Mild Method for Regioselective Labeling of Aromatics with Radioactive Iodine

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A novel technique to label *ortho*-, *meta*-, and *para*-trimethylsilyl-substituted aryl substituents with radioactive iodide is described. The method takes advantage of the *ipso*-directing and activating properties of trimethylsilyl substituents on the arenes. The method was demonstrated on a griseofulvin ana-

logue with promising anticancer properties and on lidocaine, a widely used local anesthetic drug. Treatment of a trimethylsilyl precursor with  $\text{Ti}(\text{OCOCF}_3)_3$  followed by  $\text{Na}^{125}\text{I}$  consistently afforded radioactive purities over 95 % in all cases.

### Introduction

Methods for labeling of organic molecules with radioactive isotopes of iodine, such as  $^{123}\text{I}$ ,  $^{125}\text{I}$ , and  $^{131}\text{I}$ , are important for medical applications. Iodinated drug candidates are used for screening antibodies in radioimmunoassays (RIAs)<sup>[1]</sup> and in preclinical ADME (absorption, distribution, metabolism, and excretion) studies.<sup>[2]</sup> Owing to emission of gamma radiation, iodinated radiopharmaceuticals are also used in scintigraphic imaging for disease diagnostics,<sup>[3]</sup> for example, in the localization of tumors by use of *meta*-iodobenzylguanidine (MIBG) labeled with  $^{123}\text{I}$ .<sup>[4]</sup>

The iodination of aromatics can be achieved by different methods,<sup>[5]</sup> and the choice of labeling method depends very much on the substrate. Many of the most widely used labeling techniques involve the use of oxidizing agents such as chloramine T,<sup>[6]</sup> iodogen,<sup>[7]</sup> and lactoperoxidase;<sup>[8]</sup> however, these methods suffer from low selectivity and are restricted to activated aromatics. The regioselectivity (labeling position) can be hard to control and to some extent so can the degree of labeling (the number of iodine atoms introduced). Depending on the substrate, this can result in the formation of numerous side products,<sup>[5b]</sup> which then have to be purified, often by tedious chromatographic methods.<sup>[9]</sup> Further-

more, many iodination methods are only applicable to activated aromatics, such as tyrosine in labeling of peptides and proteins.<sup>[5]</sup>

Therefore, there is a need for a broader collection of selective iodination techniques that can be performed under mild conditions. Our interest in iodination techniques arose during our search for potent analogues of the natural product griseofulvin (**1**)<sup>[10]</sup> that can inhibit centrosomal clustering in cancer cells.<sup>[11]</sup> GF-15 (compound **2**, Figure 1) was identified as one of the most active analogues,<sup>[12]</sup> and for in vivo biodistribution and half-life studies we became interested in  $^{125}\text{I}$  labeling of **2**.<sup>[13]</sup> As the activities of the three iodinated isomers of **2** (i.e., **8–10**, see Scheme 1) in a phenotypic whole-cell assay for multipolarity<sup>[11]</sup> are markedly different (data not shown), we found it crucial to apply a method that would afford a single regioisomer and thus enable us to access the *ortho*- (i.e., **8**), *meta*- (i.e., **9**), and *para*-iodo (i.e., **10**) isomers.

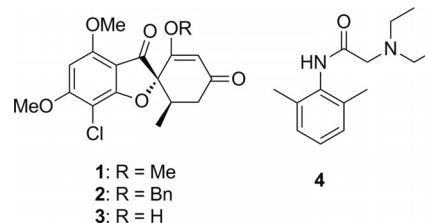


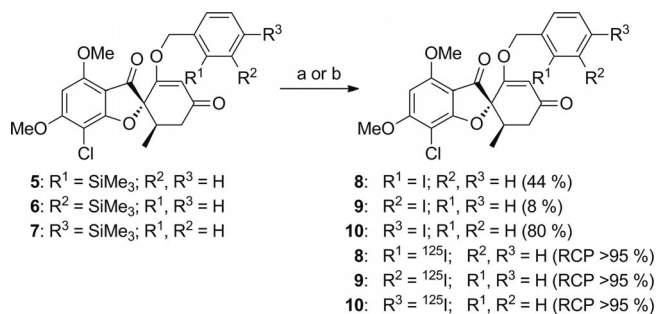
Figure 1. Structures of griseofulvin (**1**), its analogue GF-15 (**2**), griseofulvic acid (**3**), and lidocaine (**4**).

McKillop et al.<sup>[14]</sup> have introduced a method for the iodination of small aryl-containing organic molecules by the use of  $\text{Ti}(\text{OCOCF}_3)_3$  and iodide. Mechanistically, the thallated aromatics are formed by direct electrophilic metalation of the aryl ring with  $\text{Ti}(\text{OCOCF}_3)_3$ , after which ligand exchange with iodide followed by *ipso* substitution creates the aryl-iodine bond. Whereas the reaction of the

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Scheme 1. Labeling of griseofulvin analogues with <sup>127</sup>I and <sup>125</sup>I. Reagents: (a) Ti(OCOCF<sub>3</sub>)<sub>3</sub>, NaI, MeCN/TFA (7:3); (b) Ti(OCOCF<sub>3</sub>)<sub>3</sub>, Na<sup>125</sup>I, MeCN/TFA (7:3). RCP = radiochemical purity.

aryl thallium(III) bis(trifluoroacetate) intermediate with iodide affords solely the *ipso*-substituted product,<sup>[15]</sup> the initial thallation can yield mixtures of the three possible regioisomers, depending on the substrate and conditions.<sup>[16]</sup> The labeling is typically performed in pure trifluoroacetic acid (TFA).<sup>[16,17]</sup> In the case of substrates that cannot tolerate these conditions, addition of a cosolvent, such as MeCN, can usually prevent substrate degradation.<sup>[16]</sup> However, addition of a cosolvent also lowers the reactivity, which means that deactivated aromatics can be challenging to label. When we exposed griseofulvin analogue **2** to the reaction conditions [Ti(OCOCF<sub>3</sub>)<sub>3</sub> in neat TFA], hydrolysis to form griseofulvic acid (**3**, Figure 1) took place within minutes, but when milder conditions [Ti(OCOCF<sub>3</sub>)<sub>3</sub> in MeCN/TFA, 7:3] were used, no conversion of **2** was observed.

## Results and Discussion

In continuation of the work by McKillop et al., a regioselective variant of the iodination method was published by Bell et al.<sup>[18]</sup> They discovered that trimethylsilyl (TMS)-substituted aryls, such as 3-trimethylsilyltoluene, undergo *ipso* substitution when treated with Ti(OCOCF<sub>3</sub>)<sub>3</sub>, whereas none of the other regioisomers are formed above trace levels. Furthermore, the introduction of the TMS group increases the reactivity of the aromatic system, whereby less activated aryls can be thallated and iodinated. The application of this iodination technique has, to the best of our knowledge, only been used scarcely and only with nonradioactive iodine. Therefore, motivated by the work of Bell et al.<sup>[18]</sup> we hypothesized that by use of TMS-aryl **5**, **6**, and **7** (see Scheme 1), incorporation of radioactive iodine into griseofulvin analogue **2** would be possible via the corresponding thallated intermediates. To further elucidate the scope of the technique, iodination of lidocaine (**4**, Figure 1) was also investigated. Lidocaine (**4**) is a widely used local anesthetic drug, and iodination of this drug has previously been explored by El-Moselhy et al.<sup>[19]</sup>

The TMS-benzyl analogues of griseofulvin (i.e., **5–7**, Scheme 1) were synthesized from the corresponding TMS-benzyl alcohols by using known procedures (see the Supporting Information).<sup>[12]</sup>

Initially, the labeling procedure was tested with nonradioactive iodide. The three mono-TMS-analogues of griseofulvin (i.e., **5–7**) were dissolved in MeCN/TFA (7:3) and then subjected to Ti(OCOCF<sub>3</sub>)<sub>3</sub> (2 equiv.) for 30 min after which NaI (4 equiv.) was added, and the reaction mixtures were stirred for 2 min and then quenched by the addition of a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>. Gratifyingly, LCMS analysis of the reaction mixtures showed that the corresponding iodides were formed as the only product, whereas some unreacted starting material was also detected. Iodinated products **8**, **9**, and **10** were isolated by column chromatography in 44, 8, and 80% yield, respectively. The low isolated yield of **9** is due to low conversion of starting material **6** into the thallated intermediate, which presumably is a consequence of the *meta*-substitution pattern in **6**. However, for use in labeling with radioactive iodide the low conversion in the electrophilic aromatic thallation is not critical, as radioactive iodide is used in substoichiometric amounts, whereby it becomes the limiting reagent anyway (vide infra). The formation of only the *ipso*-substituted product was confirmed by comparison of the NMR spectra and the LC–MS data for iodides **8–10**, which were made through a conventional route from the corresponding iodo-benzyl alcohols (see the Supporting Information). Furthermore, the identity and uniformity of the products were verified by their retention times in HPLC analyses.

Additionally, the iodination of **7** (*para*-TMS) was tested with a lower amount of TFA (10 and 20% TFA in MeCN) but still with the use of 2 equiv. Ti(OCOCF<sub>3</sub>)<sub>3</sub> and an excess amount of NaI. At 10% TFA, the iodo product was only observed in trace amounts (LC–MS analysis), whereas at 20% TFA, the conversion to the iodo product was <20%, and this demonstrates the necessity of TFA for the reaction to occur. It was also investigated how the reaction was affected by using lower amounts of Ti(OCOCF<sub>3</sub>)<sub>3</sub> (0.9 equiv.) in MeCN/TFA (7:3), and under these conditions, the conversion of **5**, **6**, and **7** into the iodo products was 1, 5, and 20%, respectively. In complete absence of Ti(OCOCF<sub>3</sub>)<sub>3</sub>, no conversion of the starting material took place, and this underlines that protodesilylation does not occur under the conditions.

With the promising results from the iodination with <sup>127</sup>I in hand, we went on with <sup>125</sup>I labeling, in which the radioactive iodine was the limiting reagent. The labeling was performed by dissolving TMS precursors **5**, **6**, and **7** in MeCN/TFA (7:3) after which the thallation was initiated by addition of Ti(OCOCF<sub>3</sub>)<sub>3</sub> (0.5 equiv.). The reaction mixture was stirred for 2 min at 20 °C, Na<sup>125</sup>I (1.7–3.4 × 10<sup>−4</sup> equiv.) was added, and HPLC analysis was performed after 30 s. As evident from the chromatograms in Figure 2, the radiochemical purity (RCP) by HPLC for all three radioiodinations was >95%. The identity of the labeled compounds was confirmed by coelution with nonradioactive reference compounds in the HPLC analyses (detected in the UV channel).

TMS analogue **11** (see Scheme 2) of lidocaine (**4**) was synthesized in three steps from commercially available 4-bromo-2,6-dimethylaniline. For this substrate, we took ad-

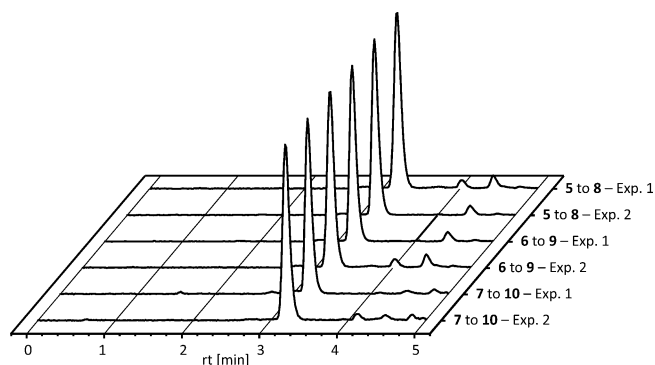
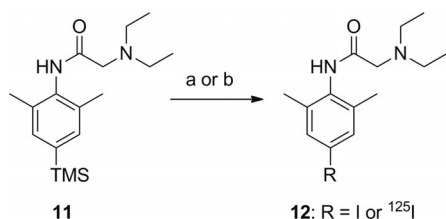


Figure 2. HPLC analysis (radio channel) of the  $^{125}\text{I}$  labeling of griseofulvin analogues **5**, **6**, and **7** into corresponding iodides **8**, **9**, and **10**, respectively.

vantage of one of the mild methods available for the introduction of a TMS group: the palladium-catalyzed cross-coupling of an aryl halide with hexamethyldisilane<sup>[20]</sup> (see the Supporting Information). The test iodination with  $\text{Na}^{125}\text{I}$  (0.5 equiv.) with the use of 0.5 equiv.  $\text{Ti}(\text{OCOCF}_3)_3$  in  $\text{MeCN}/\text{TFA}$  (7:3) gave desired iodinated lidocaine **12** (full conversion by LC–MS, see Supporting Information). The iodination also occurred if  $\text{MeCN}/\text{TFA}/\text{H}_2\text{O}$  (6:3:1) was used as the solvent mixture, which demonstrates that  $\text{H}_2\text{O}$  is tolerated in the reaction (see the Supporting Information for LC–MS analysis). Subjection of lidocaine (**4**) with no TMS group to the iodination conditions gave no iodide incorporation, whereas when neat TFA was used as the solvent, iodination was observed, and this verifies that under mild reaction conditions the TMS group is crucial for the reactivity of the aromatic ring. Performing the reaction with **11** and  $\text{Na}^{125}\text{I}$  gave the desired incorporation of  $^{125}\text{I}$  with high radiochemical purity as shown for two independent experiments in Figure 3.



Scheme 2. Iodination of TMS-lidocaine analogue **11**. Reagents: (a)  $\text{Ti}(\text{OCOCF}_3)_3$ ,  $\text{NaI}$ ,  $\text{MeCN}/\text{TFA}$  (7:3); (b)  $\text{Ti}(\text{OCOCF}_3)_3$ ,  $\text{Na}^{125}\text{I}$ ,  $\text{MeCN}/\text{TFA}$  (7:3).

The use of TMS-aryls as precursors for radioiodination has been reported previously.<sup>[5a,21]</sup> However the reported reaction conditions are rather harsh (e.g.,  $\text{NaI}$  and *tert*-butyl hypochlorite or  $\text{H}_2\text{O}_2$  in acetic acid at 60 °C) and long reaction times (>30 min) are needed to obtain reasonable conversion.<sup>[21]</sup> The need for new procedures that can transform TMS-aryls into their corresponding iodine analogue was recently demonstrated in the attempted iodination of a tomography tracer for the histamine H3 receptor, for which the use of standard reagents such as chloramine T and peracid resulted in less than 10% labeling (see the Supporting Infor-

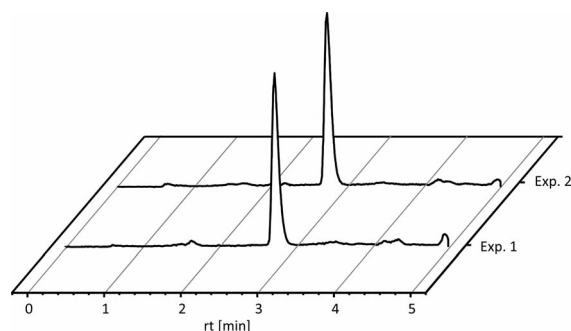


Figure 3. HPLC analysis (radio channel) of the  $^{125}\text{I}$  labeling of lidocaine analogue **11**.

mation, Scheme S1, for details).<sup>[22]</sup> Another popular method for iodination of aromatics through *ipso* substitution of an activator group is by use of arylstannanes,<sup>[5,23]</sup> which are typically converted into the corresponding aryl iodide by treatment with  $\text{NaI}$  and chloramine T (or another oxidant such as peracetic acid) in an acidic aqueous environment. Hence, the use of TMS-aryls and  $\text{Ti}(\text{OCOCF}_3)_3$  is an attractive alternative to arylstannanes, especially for molecules with low water solubility and for substrates that are sensitive to highly acidic environments (such as neat TFA) or oxidizing reagents. It is also noteworthy that the radioiodination with thallium trifluoroacetate is performed for only 30 s, which minimizes the time in which the molecules are subjected to the acidic reaction conditions.

## Conclusions

We were successful in applying the electrophilic aromatic thallation for activation of TMS-aryls in the radioiodination of a potent griseofulvin analogue and lidocaine. Radiochemical purities >95% were achieved in all cases. The conditions used are superior to those previously reported, as the iodination proceeds at ambient temperature and in a less acidic environment. Overall, this regioselective iodination method was found to be very convenient, and we envision that this procedure will be a strong alternative to the use of other labeling strategies.

## Experimental Section

**Typical Procedure for  $^{125}\text{I}$  Labeling:** The TMS-analogue (70 nmol) was dissolved in  $\text{MeCN}/\text{TFA}$  (7:3, 35  $\mu\text{L}$ ), after which a solution of  $\text{Ti}(\text{OCOCF}_3)_3$  in  $\text{MeCN}/\text{TFA}$  (7:3, 15  $\mu\text{L}$ , 2.33 mM, 35 nmol) was added. The reaction mixture was stirred for 2 min at 20 °C and then an aqueous solution of  $\text{Na}^{125}\text{I}$  (ca. 0.1  $\mu\text{L}$ , 1–2 MBq, 12–24 pmol) was added. After 2 min of stirring at 20 °C, HPLC analysis was performed.

**Safety Note:** Thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative, and  $\text{Ti}(\text{OCOCF}_3)_3$  should be handled with care in a well-ventilated fume hood.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, LC–MS data, and NMR spectra.



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